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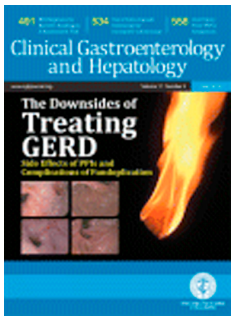

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Author Contributions:
BK: study concept and design, acquisition of data, analysis and interpretation of data, drafting the manuscript, critical revision of the manuscript
NH: acquisition of data, analysis and interpretation of data, critical revision of the manuscript
CM: acquisition of data, analysis and interpretation of data, critical revision of the manuscript
AAN: acquisition of data, analysis and interpretation of data, critical revision of the manuscript
MS: analysis and interpretation of data, critical revision of the manuscript, study supervision
HHH: study concept and design, acquisition of data, analysis and interpretation of data, drafting the manuscript, critical revision of the manuscript, study supervision

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Inflammatory bowel disease, pyoderma gangrenosum, tofacitinib

Introduction

Pyoderma gangrenosum (PG) is a difficult to treat inflammatory skin condition that affects inflammatory bowel disease (IBD) patients. There is no standardized approach for PG treatment.[1] We report the results of three patients with Crohn's disease (CD) and refractory PG, who had failed several therapies with biologics and were started on tofacitinib for severe inflammatory arthritis with resolution of their PG.

Methods

Patients were treated at the University of North Carolina-Chapel Hill between 2017 and 2018. Immunohistochemical (IHC) staining for phosphorylated JAK1, JAK2, JAK3, STAT1 and STAT3 was performed on skin biopsies from patients with known PG. Tissue samples were retrieved from a local tissue repository of the Department of Dermatology at the University Hospital Zurich. Antibodies for IHC were purchased from Abcam (Cambridge, UK) and Cell Signaling Technology (Danvers, MA, USA). IHC staining of paraffin-embedded tissue slides was performed using horseradish peroxidase method with diaminobenzidine (DAB).[2] The study was approved by the Ethics committee of UNC (18-0375).

Results

The first patient is a 49-year-old female with CD s/p colectomy with ileostomy and new-onset lower extremity PG that was refractory to therapy with golimumab, cyclosporine and ustekinumab. Due to concomitant arthritis with joint effusions, tofacitinib 5mg twice daily was initiated. Two weeks after starting tofacitinib, PG lesions improved and joint effusions subsided. By 12 weeks, all PG lesions had completely healed.

The second patient is a 24-year-old male with end ileostomy after a pouchectomy due to stricturing and fistulizing CD of the pouch. He developed peristomal PG while on vedolizumab for luminal CD. The PG was not responsive to topical or intra-lesional steroids. Due to severe arthralgias in small and large joints, he was started on tofacitinib 5mg bid while continuing vedolizumab; the arthralgias and peristomal pyoderma completely healed after 12 weeks (Figure 1 A & B).

The third patient was 34-year-old male with a 17-year history of lower extremity PG with proctectomy and colostomy for perianal CD and previous failure of two anti-TNF therapies. He developed worsening PG on his lower extremities despite well-controlled luminal disease. Ustekinumab was initiated, but the PG lesions worsened and he developed worsening arthritis with a knee effusion despite recurrent steroid tapers. Ustekinumab was discontinued and tofacitinib 5mg bid was initiated. Within a month, knee effusion, arthritis and PG lesions improved and steroids were discontinued. As PG was not completely healed, tofacitinib was increased to 10mg bid and the lesions continue to improve without need for additional steroid therapy (Figure 1 C,D).

Based on those clinical observations we aimed to confirm the role of the Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway activation in the pathogenesis of PG. We performed IHC staining in skin biopsies of two patients from a tissue repository. We detected strong staining of phospho-JAK-1, phospho-JAK-2, phospho-JAK3, phospho-STAT1 and phospho-STAT-3 in the epidermis (Figure 1 E-J). Phosphorylation is indicative for activation of the JAK/STAT molecules.

Discussion

This is the first report of successful treatment of PG with tofacitinib in IBD patients. Tofacitinib is an oral JAK1 and 3 inhibitor which is approved for the treatment of rheumatoid arthritis and ulcerative colitis and is currently being evaluated for plaque psoriasis and inflammatory arthritis.[3-6] JAK-STAT signaling is initiated when a cytokine attaches to its target cell surface receptor, which leads to phosphorylation of the receptor-associated JAK molecules followed by phosphorylation of STAT molecules, which translocate to the cell nucleus and activate transcription or suppression of target genes. The JAK/STAT pathways regulate signaling for multiple immune-relevant mediators what makes their involvement in IBD pathogenesis plausible.[7] Inflammatory arthritis was the indication for tofacitinib in all patients and the arthritis symptoms resolved in all patients within the first 2-3 weeks of therapy. Interestingly PG, which previously had been resistant to various biologics significantly improved (n=1) or completely healed (n=2). Recently, successful PG therapy with a selective JAK-2 inhibitor (Ruxolitinib) was also described.[8] With IHC staining, we found the molecular basis for success of PG treatment

with JAK inhibitors revealing activated JAK-1, JAK-2 and JAK-3 and downstream activation of STAT1 and STAT3 in PG skin lesions. These observations provide the rationale for the observed clinical findings and strongly suggest that JAK inhibitors might be a powerful approach for the treatment of PG. Further studies are warranted to further analyze the activation and regulation of the JAK-STAT pathway in PG and to investigate the efficacy of tofacitinib or more specific JAK-1 or JAK-3 inhibitors in the treatment of PG.

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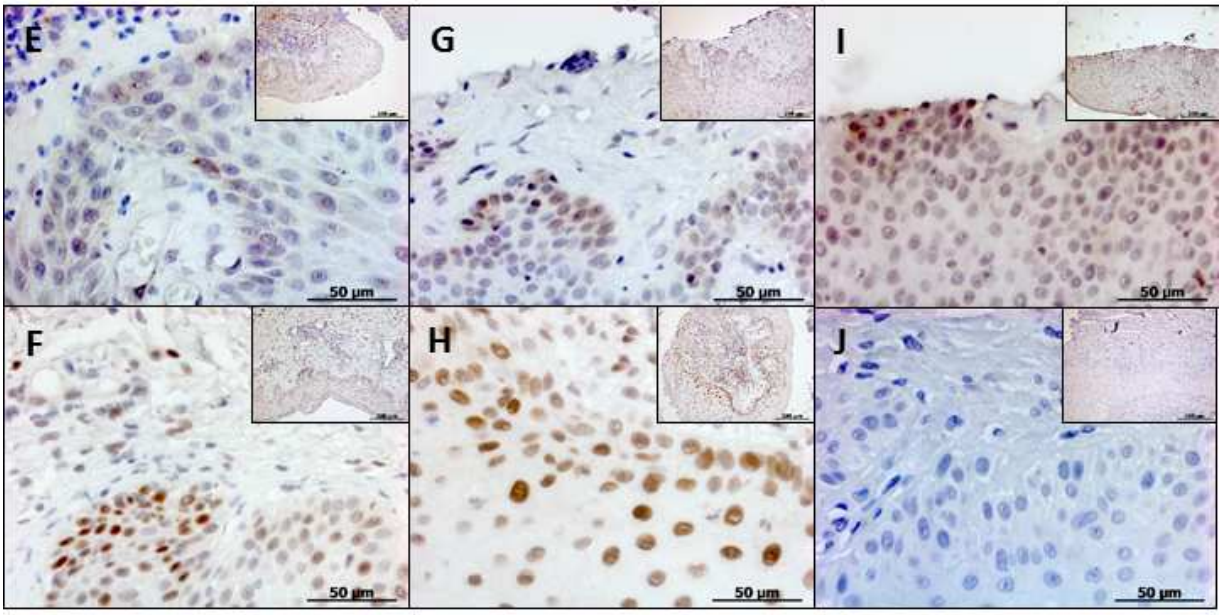
Figure legend.

Figure1: Peristomal and peripheral pyoderma gangrenosum in 2 patients before (A, C) and after (B, D) treatment with tofacitinib for 2 and 1 month, respectively. Representative images of immunohistochemical staining of phosphorylated (p) JAK1 (E), pJAK2 (G), pJAK3 (I), pSTAT1 (F), and pSTAT3 (I) and negative control (J) of Pyoderma Gangrenosum patient skin samples (IHC stains were done on slides of patient specimens derived from a tissue repository).


A
B
C
D


E
G
I
F
H
J
50 µm